Chapter 7

General discussion

GENERAL DISCUSSION

Overall summary

The focus of the present dissertation was to provide a comprehensive investigation on the association between depression and cardiovascular disease, taking into account the heterogeneity of depressive symptoms. The present dissertation was structured in two parts encompassing five chapters. The objectives of the first part were: (1) to investigate whether depressive symptom dimensions, namely cognitive/affective and somatic/affective, are differentially associated with medical prognosis in individuals with heart disease; (2) to investigate whether a general depression factor is associated with medical prognosis, independent of somatic/affective and cognitive/affective symptoms of depression unrelated to this general depression factor in individuals with myocardial infarction (MI) and; (3) to investigate the prognostic value of individual symptoms of depression in men and women of different age strata diagnosed with MI.

The objectives of the second part of the present dissertation were: (4) to investigate whether subclinical heart disease is differentially associated with depressive symptom dimensions over time in middle-aged individuals with or without depressive and anxiety disorders and (5); to investigate whether the odds for having depressive and anxiety disorders are significantly different in individuals with recognized MI as compared with individuals with unrecognized MI.

Part 1 - Depressive symptoms as prognostic markers for medical prognosis in individuals with heart disease

Several systematic reviews and meta-analyses showed that depression is associated with adverse medical prognosis in patients with

cardiovascular disease [1-4]. A limitation of these studies is that they did not account for the potential confounding effects of somatic/affective symptoms that are secondary to somatic comorbidities, but that can still be reported and interpreted as depressive symptoms. It has been suggested that not providing statistical adjustment for somatic symptoms of depression could lead to inflated total depressive symptom scores [5,6]. Several studies examined whether cognitive/affective and somatic/affective symptoms of depression are differentially associated with adverse medical prognosis (i.e. all-cause mortality, cardiovascular mortality and recurrent cardiovascular events) [7-10]. In *chapter 2,* we demonstrated through a meta-analysis of 13 studies (including 11,128 participants) that only somatic/affective symptoms and not cognitive/affective symptoms were associated with adverse medical prognosis in patients with heart disease. Moreover, several subgroup analyses were conducted. These subgroup analyses focused on studies reporting on all-cause mortality, cardiovascular mortality and recurrent cardiovascular events; but also on patients with MI and studies in which depression was assessed with the Beck's Depression Inventory (BDI). Somatic/affective symptoms of depression were consistently associated with adverse prognosis across these subgroup analyses.

In *chapter 3,* a bifactor model of the BDI was developed. This bifactor model was composed of a general depression factor, and two subgroup factors: one of somatic/affective symptoms, and the other of cognitive/affective symptoms that are unrelated to the general depression factored. This model was developed with individual-participant data (IPD) of nine studies from seven different countries, summing up to a total of 7,500 participants. The main advantage of using a bifactor model to predict prognostic endpoints in individuals with chronic disease is that it allows for modeling the multidimensionality displayed by the BDI. Although the BDI clearly measures somatic/affective and cognitive/affective symptoms [11], it has been suggested that these

depressive symptom dimensions are indicators of a common general depression factor, and that these dimensions do not reflect distinct constructs [12]. However, simply using sum scores of depressive symptoms implies the risk of yielding inflated estimates, as somatic/symptoms and cognitive/symptoms are computed equally to generate the total score [13]. Therefore, the bifactor model can be considered as a superior way to predict prognostic outcomes and to assess the multidimensionality of the BDI. Results of *chapter 3* suggested that a general depression factor was associated with adverse medical prognosis (i.e. all-cause mortality and recurrent cardiovascular events) independent of somatic/affective and cognitive/affective symptoms unrelated to the general depression factor. Moreover, it was demonstrated that somatic/affective symptoms unrelated to the general depression factor were associated with adverse medical prognosis, suggesting that treating these symptoms in individuals that are not clinically depressed, might be clinically relevant.

In *chapter 4* we investigated possible interaction effects between age, sex, and individual depressive symptoms in the association with all-cause mortality in patients with MI. A main issue with studying the association of depression with prognostic endpoints is the heterogeneity of depressive symptoms. Different individual symptoms could have different prognostic value for men and women of distinct age groups. Results presented in this chapter showed that the individual symptoms *negative body image* and *indecisiveness* were associated with all-cause mortality, but only in men 55 years or younger. Moreover, the symptom *dissatisfaction* was associated with all-cause mortality in men 56 years or older and *fatigue* was associated with all-cause mortality in men 70 years or older. In women aged between 56 and 69 years, the symptom *fatigue* was associated with all-cause mortality while in women 70 years or older, *suicidal ideation* was the only symptom associated with all-cause mortality. The association of *negative body image* and *indecisiveness* with all-cause mortality in younger men, and of *suicidal ideas* with all-cause

mortality in older women disappeared after providing statistical adjustment for left-ventricular ejection fraction (LVEF) in sensitivity analyses. Nonetheless, the association of *dissatisfaction* with all-cause mortality in older men and of *fatigue* with all-cause mortality in middle-aged/older men and older women remained statistically significant after adjusting for LVEF. These findings could be useful for clinical practice, as patients could be regarded as not being at increased risk of mortality because they are not clinically depressed, when in fact they could still be at increased risk of mortality for experiencing such symptoms.

Findings from *chapters 2, 3* and *4* suggest substantial heterogeneity in the prognostic value of specific symptoms of depression in patients with cardiovascular disease. Moreover, these findings suggest that it might be more informative to work with symptom clusters or individual symptoms instead of using sum scores. **Box 1** displays four "take-home" messages that can be learned from these three chapters.

Box 1. Take-home messages learned from the first part of the present dissertation

I. Generally, somatic/affective symptoms of depression are stronger predictors of adverse medical prognosis than cognitive/affective symptoms.

II. A general depression factor is associated with adverse cardiovascular prognosis independent of somatic/affective symptoms. However, the association is weaker than previously reported [1-4].

III. There is substantial heterogeneity regarding the prognostic value of individual depressive symptoms in men and women with MI across different age groups.

IV. Cognitive/affective symptoms seem to be particularly dangerous for younger men (i.e. aged ≤ 55 years).

Part 2 - Depressive symptoms as a consequence of cardiovascular disease

The second part of the present dissertation aimed at investigating if depressive symptoms occur as a direct consequence of cardiovascular disease. The prevalence of depression is up to two to three times higher in patients with heart disease as compared with individuals from the general population [14]. Therefore, it is important to understand the mechanisms that explain why depression is increased in individuals with heart disease.

Atherosclerosis is the main underlying cause of cardiovascular disease. Atherosclerosis consists of the thickening of the arterial walls due to the accumulation of fat, calcium and other substances in the carotid arteries. Carotid atherosclerosis can be assessed through several non-invasive ways and it has been consistently shown to be associated with the onset of cardiovascular disease [15-19]. Measures of carotid atherosclerosis can therefore be used as indicators of subclinical heart disease. In *chapter 5,* we investigated whether markers of subclinical heart disease are differentially associated with depressive symptom dimensions in patients with and without depressive and anxiety disorders. Findings of this chapter suggest that augmentation index (a measure of arterial stiffness) was modestly associated with both depressive symptom dimensions. As the estimates for both depressive symptom dimensions were comparable, it is unlikely that there is a differential association of subclinical heart disease and depressive symptom dimensions. The other markers of subclinical heart disease (i.e. carotid intima-media thickness [CIMT] and presence of plaque in the carotid arteries) were not associated with any of the depressive symptom dimensions.

In *chapter 6,* we investigated whether the odds of having depressive and anxiety disorders are increased in individuals aware of

their MI compared with individuals who are not aware of having had a MI (i.e. individuals with an unrecognized MI). We demonstrated that the odds of having anxiety and depressive disorders in individuals with recognized MI is significantly higher than in individuals without MI. However, the risk of having anxiety and depressive disorders in individuals with unrecognized MI is not significantly increased as compared with individuals without MI. Statistical adjustment for health-related quality of life seemed to explain the increased risk for having depressive disorders in individuals with recognized MI, however, it did not explain the increased odds for having anxiety disorders.

Based on the findings of *chapter 6*, it can be speculated that the increased prevalence of depression and anxiety in individuals with heart disease can be largely explained by the psychological burden associated with receiving a diagnosis of a severe chronic disease. Although there are biological mechanisms explaining the association between heart disease and depression, it seems that the risk is not significantly increased in individuals who are not aware of their condition (i.e. individuals with unrecognized MI or with increased levels of subclinical heart disease). Moreover, a recognized MI is generally more symptomatic than an unrecognized MI, and therefore associated with an increased medical burden, which could also explain the increased odds for depression and anxiety in individuals with recognized MI. Nonetheless, more prospective longitudinal studies are necessary to come to a conclusion.

Implications for clinical practice

Findings reported in the present dissertation can be useful for researchers devoted to develop new interventions for treating depressive symptoms in patients with heart disease. To date, it has been reported that psychotherapy and psychopharmacological (i.e. antidepressants) interventions have a small but clinically significant effect on decreasing depressive symptomatology in patients with CHD[20]. Nonetheless, solely receiving treatment did not show to efficiently improve medical prognosis in patients with CHD. However, when levels of depressive symptoms decreased, then the prognosis significantly improved [21].

Implications for clinical practice in the first part of the thesis

As reported in *chapter 2*, somatic/affective symptoms are significantly associated with adverse medical prognosis in patients with heart disease, but cognitive/affective symptoms are not. Not surprisingly, authors of a previous study found that changes in somatic/affective symptoms were related to the prognostic outcomes (all-cause mortality, cardiovascular mortality and recurrent cardiovascular events), but changes in cognitive/affective symptoms were not[22]. Therefore, it can be concluded that interventions focusing on treating somatic/affective symptoms of depression are highly warranted in patients with MI.

Treating certain individual depressive symptoms is also highly warranted depending on the patient's profile. It was demonstrated in *chapter 4* that fatigue is the depressive symptom most often reported in patients with MI. Moreover, fatigue is associated with all-cause mortality in men 56 years or older and in women aged between 56 and 69 years, independent of risk factors of heart disease severity. Moderate aerobic exercise has been shown to decrease fatigue[23]. Promoting physical activity in individuals with heart disease may be an efficient and cost-

effective way to treat depression in individuals with cardiovascular disease [24-26]. Nonetheless, clinicians should also be aware that some patients might be reluctant to engage in exercising. Authors of future studies should compare whether specific types of exercise have differential beneficial efficacy across different individuals (e.g. such as comparing endurance with strength/resistance exercise modalities).

Depression is a pleiomorphic disorder, therefore, it should not be expected that "one-size fits all" solutions are effective. Although somatic/affective symptoms seem to be the most cardiotoxic among depressive symptoms, treating cognitive/affective symptoms is also important since cognitive/affective symptoms are related to a high burden of disease and decreased quality of life. Moreover, according to the results presented in *chapter 4*, interventions focused on treating cognitive symptoms, especially negative body image and indecisiveness could be beneficial for middle-aged men (<55 years) with regard to improving medical prognosis. Findings from a meta-analysis suggested that stand-alone CBT for body image significantly improves negative body image [27]. This intervention includes a combination of cognitive restructuring, self-monitoring and psychoeducation aimed at dysfunctional cognitions, with the objective to improve exposure, response prevention and desensitization of the participant in the way that the individual progressively stops experiencing a negative image of himself or herself. Future studies should assess whether these interventions significantly improve survival in patients with MI.

Implications for translating the present findings to clinical practice

As suggested in *chapter 6,* depression is significantly increased in individuals who are aware of their MI, as compared to individuals with an unrecognized MI or without MI. The psychological burden associated with

receiving a diagnosis of a chronic disease, and also the traumatic experience of having a heart attack could pose as potential explanatory mechanisms for this increased odds for depression [29]. Patients recently diagnosed with MI should get direct access to psychological treatment. A new and cost-effective strategy is blended e-health. It consists of a combination of online and face-to-face care [30,31]. Recent findings of a RCT showed that individuals with common mental disorders receiving blended e-health returned to work faster than individuals receiving care as usual. One potential advantage of blended e-health is the possibility of improving the communication between patient and clinician. Authors of future studies should design and test blended e-health interventions focused on individuals with MI and see whether it can improve not just depressive symptoms but also cardiovascular endpoints.

Disease beliefs are also important factors explaining the increased depressive symptomatology among patients with heart disease. Cardiac misconceptions (a specific form of disease beliefs) stand for the tendency that some patients have, to excessively perceive their cardiac disability despite already being partially physically recovered. Increased cardiac misconceptions have been shown to be associated with anxiety and depression[32]. Several randomized controlled trials aiming to assess interventions to change cardiac misconceptions have been conducted in individuals with CHD. Authors of a systematic review of the literature reported that tailoring interventions to change cardiac misconceptions is possible, and that cognitive-behavioral therapy and counseling interventions seem to be the most effective ways to reduce cardiac misconceptions[33]. Therefore, cardiac rehabilitation programs should include interventions to change cardiac misconceptions in patients with heart disease when necessary.

In summary, several clinical recommendations regarding treating depression in individuals with heart disease can be extracted from the present dissertation. **Box 2** lists these clinical recommendations.

Box 2. Summary of clinical implications for depression treatment in individuals with heart disease

I.	Somatic/affective but not cognitive/affective depressive symptoms should be the main focus of interventions aiming to treat depressive symptoms in individuals with heart disease.
II.	Physical activity may significantly decrease somatic/affective symptoms of depression.
III.	Tailor-made treatments are preferable in opposition to "one-size fits all" treatments.
IV.	Psychological support must be provided for patients immediately after receiving a diagnosis of MI when necessary
V.	Interventions aimed at changing cardiac misconceptions should be provided when necessary. Clinicians should be aware of how patients conceptualize their disease.

Recommendations for future research

In this section, considerations for future research are made, based on the findings reported throughout the dissertation.

As demonstrated in *chapter 2*, several studies assessing the prognostic value of depressive symptom dimensions in patients with heart disease have been conducted. Substantial methodological heterogeneity was found between these studies, especially regarding the way depressive symptom dimensions were derived. To improve the comparability between these studies, authors of future studies should establish a standard depressive symptom factor structure in patients with heart disease. In *chapter 3*, we proposed a bifactor model of the Beck's Depression Inventory (BDI) that simultaneously estimates scores for a general depression factor and for cognitive/affective and

somatic/affective symptom dimensions that are unrelated to the general depression factor.

The adverse prognostic effect of depressive symptoms has been demonstrated in individuals with several chronic conditions such as cancer, chronic obstructive pulmonary disease (COPD), kidney disease, diabetes and individuals subjected to organ transplantation [34-36]. However, the differential association of depressive symptom dimensions and medical prognosis has still not been widely investigated in patients with these chronic conditions. Conducting secondary analyses of data of studies that were already published could address this gap. IPD meta-analysis is preferable for this purpose, as this approach allows for the standardization of the analyses [37]. Mixed-effects multivariable predictive models are also preferable, as they can account for the between-studies variability and allow for multivariate statistical adjustment of factors that are known to confound the association between depression and prognostic outcomes in individuals with somatic diseases (e.g. disease severity, demographics, comorbidity).

None of the individual depressive symptoms appear to be significantly associated with all-cause mortality in younger women with MI (chapter 4). Future studies should focus on understanding the mechanisms that protect younger women with MI from the adverse effects of depressive symptoms.

To date, the association between the recognition of a MI and the occurrence of anxiety disorders has only been investigated in a cross-sectional design. Authors of future studies should investigate whether the risk of having anxiety disorders is increased in individuals with recognized MI using prospective longitudinal designs. Moreover, future studies should also investigate whether there is a differential association between MI status and symptom dimensions of depression and anxiety.

Authors of future studies could perform secondary analyses on existing data of clinical trials aiming at treating depression in patients with heart disease. These secondary analyses could focus on assessing possible interaction effects on treatment efficacy (e.g. to assess whether younger or older patients might benefit more from a specific treatment) with regard to both medical and psychological outcomes. In the last decades, a large amount of data from studies on depressive symptoms and heart disease has been produced. If researchers are able to invest time on data stewardship, by making these data findable, accessible, interoperable and reusable, many new research questions could be answered and replicated without the need of collecting new data[38]. Moreover, researchers that are going to start collecting data should also better address data stewardship and take the long-term preservation of their data into account, so that it can be more often reused[38].

Limitations of the present dissertation

The present dissertation has several methodological limitations. In this section, an attempt to summarize these limitations was made.

The main limitation of *chapter 2* was the substantial heterogeneity across the studies included in the meta-analysis[39]. The studies pooled in *chapter 2* used different techniques to derive depressive symptom dimensions, different covariate adjustments and included different endpoints (i.e. all-cause mortality, cardiovascular mortality, cardiovascular events and composites of these). IPD meta-analysis is an efficient way to overcome these limitations, as it allows for standardization of the statistical analyses [37].

In *chapter 3*, limitations were also encountered. First, not every individual study that was included in the sample had collected data on all markers of cardiac disease severity, such as LVEF and Killip Class. Including LVEF and Killip Class in the analyses led to a decrease of 41% of

the total sample size. Moreover, we did not use multilevel confirmatory factor analysis (CFA) to generate the bifactor model of the BDI, as this could have led to inaccurate results due to small group-level size (N < 100) [40]. Nonetheless, we attempted to account for the multilevel structure of the sample by conducting a multiple indicators multiple causes (MIMIC) model. This model consists of a traditional CFA in which the adjustment of multiple covariates (in our case, a variable representing different study levels) is possible. Another important limitation of *chapter 3* was the strategy to handle missing data of the BDI items. As a large proportion of the sample already had imputed missing data using mean imputation, we followed the same procedure, which might not be the optimal approach. Nonetheless, previous studies comparing different imputation methods have suggested that mean imputation can be preferable to more complex methods for certain applications [41].

An important limitation of *chapter 4* was that we did not measure depressive symptoms with the actual BDI 10 (a shortened version of the BDI). Instead, we adapted the original BDI to the BDI10. Besides having less items, the BDI10 displays its response categories on a three-point Likert scale, while the original BDI displays it on a four-point liker scale [42]. For this purpose, we had to manually reduce the numbers of item response categories. Ideally, the data should have been recorded with three response categories. Another important limitation of this chapter was that no formal hypothesis on the predictive value of the individual symptoms of depression was made. Therefore, as many analyses were conducted, the problem of multiple testing could be present (i.e. finding significant associations by chance due to the increased number of statistical tests).

Findings of *chapter 5* should also be interpreted in the light of study limitations. The sample size of this study was substantially smaller than the ones used in previous longitudinal studies investigating the association between subclinical heart disease and depressive symptoms.

This could have led to reduced statistical power [43,44]. In chapter 5, the mean age of the sample was also substantially lower than of previous reports, and atherosclerosis is significantly more prevalent in the elderly. An important strength of this study was the use of longitudinal analyses by making use of mixed models.

In *chapter 6,* important limitations were also present. The cross-sectional study design does not allow making inferences on causality. However, despite this limitation, our findings replicated the results of a previous prospective study assessing the risk of having depressive disorders associated with MI recognition [29] in a larger sample size. Another relevant limitation of *chapter 6* was the potential misclassification of diagnosing an unrecognized MI. Nonetheless; we tried to validate the group of participants diagnosed with unrecognized MI by comparing whether they were significantly different from participants without MI regarding typical risk factors for MI (e.g. age, sex, diabetes and health-related quality of life). Moreover, another limitation of the study was that psychiatric disorders were assessed with the Mini neuropsychiatric interview (MINI). Although considered valid and reliable, clinicians do not administer the MINI self-report questionnaire, and this could have compromised the validity of the diagnoses in this study.

Concluding remarks

This thesis demonstrated that general depression is a predictor of adverse medical prognosis in patients with heart disease; even after accounting for the confounding effect of somatic/affective symptoms not related to general depression. However, the association between depression and medical prognosis in patients with MI is weaker than previously reported, when no adjustment was performed for these somatic/affective symptoms. Somatic/affective symptoms of depression

are in general more dangerous than cognitive/affective symptoms. However, cognitive/affective symptoms, such as indecisiveness and negative body image, seem to be related to an adverse medical prognosis in men 55 years or younger. Authors of future studies should tailor new interventions for specific age groups focusing on treating individual depressive symptoms that are more cardiotoxic, instead of focusing on "one-size fits all" treatments.

In addition, we found that the biological factors linked to heart disease do not seem to be the main reason leading to increased depressive symptomatology. Apparently, the psychological burden that is associated with receiving a diagnosis of a heart disease is more likely to explain the increased risk of having depression in individuals with heart disease. However, care should be taken before making final conclusion in the light of study limitations and results should be replicated in studies with a prospective design.

References

1. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: A meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *Eur Heart J*. 2006;27(23):2763-2774.

2. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: A meta-analysis. *Psychosom Med*. 2004;66(6):802-813.

3. Meijer A, Conradi HJ, Bos EH, et al. Adjusted prognostic association of depression following myocardial infarction with mortality and cardiovascular events: Individual patient data meta-analysis. *Br J Psychiatry*. 2013;203:90-102.

4. Meijer A, Conradi HJ, Bos EH, Thombs BD, van Melle JP, de Jonge P. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: A meta-analysis of 25 years of research. *Gen Hosp Psychiatry*. 2011;33(3):203-216.

5. Ormel J, De Jonge P. Unipolar depression and the progression of coronary artery disease: Toward an integrative model. *Psychother Psychosom*. 2011;80(5):264-274.

6. Delisle VC, Arthurs E, Abbey SE, et al. Symptom reporting on the beck depression inventory among post-myocardial infarction patients: In-hospital versus follow-up assessments. *J Psychosom Res*. 2012;73(5):356-361.

7. De Jonge P, Ormel J, Van DB, et al. Symptom dimensions of depression following myocardial infarction and their relationship with somatic health status and cardiovascular prognosis. *Am J Psychiatry*. 2006;163(1):138-144.

8. Martens EJ, Hoen PW, Mittelhaeuser M, de Jonge P, Denollet J. Symptom dimensions of post-myocardial infarction depression, disease severity and cardiac prognosis. *Psychol Med*. 2010;40(5):807-814.

9. Connerney I, Sloan RP, Shapiro PA, Bagiella E, Seckman C. Depression is associated with increased mortality 10 years after coronary artery bypass surgery. *Psychosom Med*. 2010;72(9):874-881.

10. Roest AM, Thombs BD, Grace SL, Stewart DE, Abbey SE, de Jonge P. Somatic/affective symptoms, but not cognitive/affective symptoms, of depression after acute coronary syndrome are associated with 12-month all-cause mortality. *J Affect Disord*. 2011;131(1-3):158-163.

11. Beck AT, Steer RA. *Beck depression inventory: Manual.* New York: Psychological Corporation; 1987.

12. Carney RM, Freedland KE. Are somatic symptoms of depression better predictors of cardiac events than cognitive symptoms in coronary heart disease? *Psychosom Med*. 2012;74(1):33-38.

13. DiStefano C, Zhu M, Mindilã D. Understanding and using factor scores: Recommendations for the applied researcher. *Practical Assessment, Research & Evaluation*. 2009;14(20):1-11.

14. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: A clinical review. *Eur Heart J*. 2014;35(21):1365-1372. doi: 10.1093/eurheartj/eht462.

15. Seldenrijk A, van Hout HP, van Marwijk HW, et al. Carotid atherosclerosis in depression and anxiety: Associations for age of depression onset. *World J Biol Psychiatry*. 2011;12(7):549-558.

16. Kitamura A, Iso H, Imano H, et al. Carotid intima-media thickness and plaque characteristics as a risk factor for stroke in japanese elderly men. *Stroke*. 2004;35(12):2788-2794.

17. Chambless LE, Folsom AR, Clegg LX, et al. Carotid wall thickness is predictive of incident clinical stroke: The atherosclerosis risk in communities (ARIC) study. *American Journal of Epidemiology*. 2000;151(5):478-487.

18. Adji A, O'Rourke MF, Namasivayam M. Arterial stiffness, its assessment, prognostic value, and implications for treatment. *American Journal of Hypertension*. 2011;24(1):5-17.

19. Sakuragi S, Abhayaratna WP. Arterial stiffness: Methods of measurement, physiologic determinants and prediction of cardiovascular outcomes. *Int J Cardiol*. 2010;138(2):112-118.

20. Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with diabetes mellitus and depression. *Cochrane Database Syst Rev*. 2012;12:CD008381.

21. Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with coronary artery disease. *Cochrane Database Syst Rev*. 2011;(9):CD008012. doi(9):CD008012.

22. Roest AM, Carney RM, Freedland KE, Martens EJ, Denollet J, de Jonge P. Changes in cognitive versus somatic symptoms of depression and event-free survival following acute myocardial infarction in the enhancing recovery in coronary heart disease (ENRICHD) study. *J Affect Disord*. 2013.

23. Sandor B, Nagy A, Toth A, et al. Effects of moderate aerobic exercise training on hemorheological and laboratory parameters in ischemic heart disease patients. *PLoS One*. 2014;9(10):e110751.

24. Blumenthal JA, Sherwood A, Babyak MA, et al. Effects of exercise and stress management training on markers of cardiovascular risk in patients with ischemic heart disease: A randomized controlled trial. *JAMA*. 2005;293(13):1626-1634.

25. Blumenthal JA. Depression and coronary heart disease: Association and implications for treatment. *Cleve Clin J Med*. 2008;75 Suppl 2:S48-53.

26. Blumenthal JA, Sherwood A, Babyak MA, et al. Exercise and pharmacological treatment of depressive symptoms in patients with coronary heart disease: Results from the UPBEAT (understanding the prognostic benefits of exercise and antidepressant therapy) study. *J Am Coll Cardiol*. 2012;60(12):1053-1063.

27. Jarry JL, Ip K. The effectiveness of stand-alone cognitive-behavioural therapy for body image: A meta-analysis. *Body Image*. 2005;2(4):317-331.

28. Campbell A, Hausenblas HA. Effects of exercise interventions on body image: A meta-analysis. *J Health Psychol*. 2009;14(6):780-793.

29. Jovanova O, Luik AI, Leening MJ, et al. The long-term risk of recognized and unrecognized myocardial infarction for depression in older men. *Psychol Med*. 2016:1-10.

30. Smeets O, Martin Abello K, Zijlstra-Vlasveld M, Boon B. E-health within the dutch mental health services: What is the current situation? *Ned Tijdschr Geneeskd*. 2014;158:A8589.

31. Volker D, Zijlstra-Vlasveld MC, Anema JR, et al. Effectiveness of a blended web-based intervention on return to work for sick-listed employees with common mental disorders: Results of a cluster randomized controlled trial. *J Med Internet Res*. 2015;17(5):e116.

32. Furze G, Bull P, Lewin RJP, Thompson DR. Development of the york angina beliefs questionnaire. *Journal of Health Psychology*. 2003;8(3):307-315.

33. Goulding L, Furze G, Birks Y. Randomized controlled trials of interventions to change maladaptive illness beliefs in people with coronary heart disease: Systematic review. *J Adv Nurs*. 2010;66(5):946-961.

34. Dew MA, Rosenberger EM, Myaskovsky L, et al. Depression and anxiety as risk factors for morbidity and mortality after organ transplantation: A systematic review and meta-analysis. *Transplantation*. 2015;100(5):988-1003.

35. Falagas ME, Zarkadoulia EA, Ioannidou EN, Peppas G, Christodoulou C, Rafailidis PI. The effect of psychosocial factors on breast cancer outcome: A systematic review. *Breast Cancer Research*. 2007;9(4):1.

36. Cuijpers P, Vogelzangs N, Twisk J, Kleiboer A, Li J, Penninx BW. Comprehensive meta-analysis of excess mortality in depression in the general community versus patients with specific illnesses. *Am J Psychiatry*. 2014.

37. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: Rationale, conduct, and reporting. *BMJ*. 2010;340:c221.

38. Wilkinson MD, Dumontier M, Aalbersberg IJ, et al. The FAIR guiding principles for scientific data management and stewardship. *Sci Data*. 2016;3:160018.

39. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560.

40. Hox JJ, Maas CJM. The accuracy of multilevel structural equation modeling with pseudobalanced groups and small samples. *Structural Equation Modeling: A Multidisciplinary Journal*. 2001;8(2):157-174.

41. Baker J, White N, Mengersen K. Missing in space: An evaluation of imputation methods for missing data in spatial analysis of risk factors for type II diabetes. *Int J Health Geogr*. 2014;13:47-072X-13-47.

42. Denollet J, Martens EJ, Smith OR, Burg MM. Efficient assessment of depressive symptoms and their prognostic value in myocardial infarction patients. *J Affect Disord*. 2010;120(1-3):105-111.

43. Newson RS, Hek K, Luijendijk HJ, Hofman A, Witteman JC, Tiemeier H. Atherosclerosis and incident depression in late life. *Arch Gen Psychiatry*. 2010;67(11):1144-1151.

44. Prugger C, Godin O, Perier M, et al. Longitudinal association of carotid plaque presence and intima-media thickness with depressive symptoms in the elderly: The three-city study. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2015;35(5):1279-1283.